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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,809	07/03/2001	Raghavan Rajagopalan	MRD/63	5120

26875 7590 12/16/2003

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EXAMINER

MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/898,809

Applicant(s)

RAJAGOPALAN ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on an interview of 11/7/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,11-14 and 23-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 2 11-14 23-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☒ Interview Summary (PTO-413) Paper No(s). 12.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an interview held with John Doll on 11/7/03. There are fifteen claims pending and fifteen under consideration. Claims 1 and 12 have been amended. Claims 3-10 and 15-22 have been cancelled. Claim 31 is new. Claims 1, 2, and 11 are composition claims. Claims 12-14 and 23-31 are use claims. This is the fourth action on the merits. The application concerns some cyanine dye compositions and uses thereof.

Response to Amendment

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

3. The amendments of 8/11/03, paper #9, have been entered and are the basis for this action.

4. Applicants' cancellation of the non-elected claims renders moot the objection made in point #3 of the Final Rejection, paper #8 of 5/14/03. Applicants' amendment concerning the non-elected subject matter overcomes the objection made in point #4 of that action.

5. The declaration by Dr. Rajagopalan, a fellow Columbia University alumnus, under 37 CFR 1.132 filed 2/27/03 is sufficient to overcome the rejection of claims 1, 2, 11-14, and 23-30 based upon indefiniteness of the word "cyanine". This is the

subject of points #3-#9 of the declaration. The indefiniteness rejection was made in the first action on the merits, in paper #5. The rejection was withdrawn in the Final rejection in paper #8. The Examiner is including this for the sake of completeness.

6. The declaration by Dr. Rajagopalan under 37 CFR 1.132 filed 2/27/03 is insufficient to overcome the rejection of claims 1, 2, 11-14, and 23-30 based upon indefiniteness and lack of description as set forth in points #6 and #11 of the Final Rejection, paper #8 of 5/14/03. This is the subject of points #10-#15 of the declaration. While the biological function of these radicals is clear, nowhere does this declaration state what the structures of these radicals are. Nowhere does the declaration point to literature sources explaining that the relationship between the biological functions in the claim limitations and the structure of the radicals is art-recognized. Throughout these points, Dr. Rajagopalan uses the word "epitope", stating radical E is an epitope, which can be a "peptideomimetic, a carbohydrate, a glycomimetic, a drug, a hormone, or a nucleic acid". Epitope is not a claim limitation and the art accepted definition of epitope is "[t]he particular site within a macromolecule to which a specific antibody binds", (Life Science Dictionary). Carbohydrates, drugs, hormones, nucleic acids, and single amino acids are all incapable of forming antibodies and cannot be epitopes. In point #12 any molecule

that binds to the estrogen receptor is offered as an estrogen receptor-binding molecule. Well, yes but what is the structure or where is the evidence that the skilled chemist would immediately understand the correlation between structure and function of such estrogen receptor binding molecules. In point #14 cholecystekinin is offered as a "cholecystekinin receptor-binding molecule". Yes, but what other radicals formed from molecules binding to this receptor are being claimed? Many such compounds exist, but what are they and where in the specification are their structures described? Mere allegations are not probative. *In re CHILOWSKY*, 134 USPQ 515, "[i]n this respect they are not only expressions of opinion but incompetent expressions. We have been unable to find in the facts which the affidavits support a basis for deciding that Chilowsky has complied with the requirements of section 112.", *In re LINDELL*, 155 USPQ 521.

7. The declaration by Dr. Rajagopalan under 37 CFR 1.132 filed 2/27/03 is insufficient to overcome the rejection of claims 1, 2, 11-14, and 23-30 based upon lack of enablement point #10 of the Final Rejection, paper #8 of 5/14/03. This is the subject of points #16-#18 of the declaration. Nowhere does the declaration point to literature sources explaining how to make all of these functionally described radicals. For example, while no such explanation is required of how to make cholecystekinin, how is one to prepare all of the remaining "cholecystekinin

receptor binding molecule[s]" whose structures are not found in the specification? Mere allegations are not probative. *In re CHILOWSKY*, 134 USPQ 515, "[i]n this respect they are not only expressions of opinion but incompetent expressions. We have been unable to find in the facts which the affidavits support a basis for deciding that Chilowsky has complied with the requirements of section 112.", *In re LINDELL*, 155 USPQ 521.

Claim Rejections - 35 USC § 112

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1, 2, 11-14, 23-30 remain rejected and claim 31 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" are all indefinite for two reasons. "E" cannot be a molecule, which lacks any free valence, it must be a univalent radical.

9. Secondly, what are the chemical structures of these fragments that define radical "E"? These are not art-recognized structural terms. The passage spanning line 17, page 12 to line 12, page 13 lists the function that these radicals are to perform, but does not clarify the molecular structures. Applicants' statement that "E" is an epitope only further clouds the issue. The Examiner understands that an

epitope is a portion of a macromolecule chain capable of forming an antibody. Is “E” an antibody or only a short peptide segment from an antibody? If only macromolecules can be epitopes, then how can steroid hormones and amino acids be epitopes? Are the synthetic biomolecules listed in lines 11-13, page 13 “E”?

10. Claims 1, 2, 11-14, 23-30 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specific phrase “carbohydrate receptor-binding molecule” is indefinite. There is an entire class of such carbohydrate receptors, quite possibly thousands, and generally poorly understood and characterized. How would one know if any molecule E bound to such a receptor without checking all such receptors?

11. What does “associated with biomolecules” mean in claim 11 in Applicants definition of “E”. Are Applicants’ claiming these substances, or antibodies to these? Must “E” be a peptide segment of an antibody or can it be a hormone, amino acid etc?

These four indefiniteness rejections will be considered together. Applicants point to two passages in the specification lines 17-18, page 12 and line 21, page 14 to line 2, page 15 as clarifying the structure of the radicals they claim and refer to a declaration by Dr. Rajagopalan. This is not persuasive. Firstly, the passages, to

which applicants point, define the function of the radicals they claim. The passages contain open language, "for example" and give limited directions for how to even find such radicals. Direction to seek such radicals does not substitute for chemical formulas giving the structures of such radicals. Secondly, Search of the US Patent full text file for the phrases reveals only five previous uses, in US Patent 6,485,704 B1 and in published applications, US 20030072763 A1, US 20030036538 A1, US 20030017164 A1, US 20020169107 A1, and US 20020164287 A1. All of these are by the present Applicants. While the phrases may be understood in the Applicants' own laboratory, no other scientists would know what radicals are intended. Thirdly, the declaration by Dr. Rajagopalan was discussed above.

12. Claim 11 recites the limitation "associated with ... monoclonal antibodies, polyclonal antibodies, receptors [and] receptor binding molecules" in lines 5 and 6. There is no antecedent basis for this limitation in the parent claim 1, which lists seven specific receptors, not all receptors or all molecules that bind to any receptor. This would require testing all antibodies to every antigen to determine what is included by this claim.

Applicants make no specific argument concerning this rejection. The Examiner is considering this separately because claim 11 is simply broader in

scope than the parent claim upon which it depends, independently of the meaning of the terms in the parent claim.

13. Claims 1, 2, 11-14, 23-30 remain rejected and claim 31 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparing compounds with radical "E" being dihydroxyindolecarboxylic acid or the peptide Cytate, does not reasonably provide enablement for preparing all the other functionally described E binding molecules. The specification does not enable any person skilled in the art of organic synthesis to make the invention commensurate in scope with these claims.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims." *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) If E is an epitope from an antibody, raising all possible antibodies to the somatostatin receptor and locating all the possible epitope sites on these antibodies is an impossible task. Alternatively, screening all "hormones, amino acids,

peptides, ... and aptamers” to determine if they bind to the receptors listed in claim 1 is an open-ended and potentially inconclusive research project. Locating the epitope on any particular antibody to a somatostatin receptor say, would a moderate degree of experimentation. However, all possible antibodies would have to be made because the individual epitope sites would differ. After this is done, each individual radical would have to be synthesized in a form that would allow attachment to the rest of the pictured molecule. Thus, the degree of experimentation required is huge. b) The direction concerning the compounds claimed is found in Figure 2. In that figure, the radical “E” is described as “Biomolecule”. Thus, Figure 2 does not appear to be a working example. There is neither direction given concerning the synthesis of "biomolecule" nor its attachment to the rest of the claimed formula. c) There are no working examples of a compound of formula given in claim 1. There is no procedure given to determine the affinity of any substance to the receptors listed in claim 1. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art for tumor binding agents is given in the references spanning line 22, page 13 to line 5, page 14. f) The artisan using Applicants invention to prepare the compounds whose use is claimed would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g)

Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all the presently unknown list of functionally described radicals E embraced by claim 1. Reference AR teaches the use of an octapeptide which binds to the somatostatin receptor. A radical which derived from this peptide would fit the definition of “E” but is unclear if there additional such peptides or how the peptide Cytate was identified. The scope of the claimed subjected matter, as far as the “E” radical, is enormous.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Applicants argue that the declaration discussed above provides enablement and focusing upon steroids argue that the skilled medicinal chemist understands the structures of steroids. The declaration was discussed above. The argument concerning steroids is not persuasive for three reasons. Firstly, the claim limitation

is "steroid receptor binding molecules". Not all compounds that bind to a steroid receptor are steroids. For example, diethyl stilbesterol (DES) does not contain the cyclopentylphenanthrene ring system of the steroid, yet DES binds to the estrogen steroid receptor. In fact, a cottage industry has sprung up searching successfully for non-steroidal compounds that bind to the estrogen receptor with *presumably toxic effects*. Secondly, Applicants are reminded of the fact situation of *In re Kirk and Petrow*, 153 USPQ 48, where the U.S. Court of Customs and Patent Appeals held,

"it is appropriate to note that the specification does not even intimate that the claimed compounds of the spirostane and pregnane series themselves have "biological activity," much less the specific progestational, glucocorticoid or anti-inflammatory activities mentioned in the affidavit. With respect to the eighteen androstanes that are disclosed, five of which are claimed here, it is said they "are of value * * * in some cases on account of their biological properties." (Emphasis supplied.) There is no suggestion which androstanes are of value for that reason, or what biological properties make them useful." Spirostane, pregnane, and androstanes are all steroids. Applicants are reminded of the legal conclusion reached in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 by the U.S. Court of Appeals Federal Circuit,

"[a] description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function".

Thirdly, directions to the biochemist for how to search for molecules meeting Applicants' functional limitations, do not substitute for direction to the organic process chemist of how to make Applicants' claimed radicals.

14. Claims 1, 2, 11-14, 23-30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The issue concerning the meaning of phrases "somatostatin binding molecule" ... "carbohydrate binding molecule" *etc* are discussed above.

According to the MPEP §2163 I. A.

"the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art."

The MPEP states in §2163 II 3. ii)

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.”

Applicants have disclosed no species and have made no assertion that there is any known or disclosed correlation between the function of radical “E” and its structure.

Applicants correctly point out that this issue is factually related to the indefiniteness issue of the meaning of "somatostatin receptor binding molecules" *etc.* The examiner agrees but asserts a distinct legal issue is involved, namely if Applicants know the structures of the molecules they are attempting to patent. Applicants do assert that the skilled medicinal chemist would understand the structures involved but provide no evidence to that point. The Examiner has presented evidence that the meaning is not widely understood. Applicants are reminded of the legal conclusion reached in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 by the U.S. Court of Appeals Federal Circuit,

"We next address Enzo's additional argument that the written description requirement for the generic claims is necessarily met as a matter of law because the claim language appears in *ipsis verbis* in the specification. We do not agree. Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement."

15. Claims 12-14 and 23-30 remain rejected and claim 31 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any "target tissue" or treating any human disease. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection have been summarized above.

a) Determining if any particular claimed compound would treat any particular target tissue disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating diseases is found in the passage spanning line 10, page 8 to line 7, page 9, which merely states Applicants' intention to do so. In lines 14-16, page 2, line 18, page 2, and the lines spanning line 22, page 2 to line 2, page 3 Applicants discuss specific diseases amenable to photo therapy.

Applicants describe formulations in the passages spanning line 11, page 16 to line 2, page 17 and line 17, page 17 to line 5, page 18. There is no working example of any formulation required to practice Applicants intended therapies. Doses required to practice their invention are described in lines 2 and 3, page 17. A 5,000-fold range of doses is recommended. Since no cyanine dye linked to the mercaptooxy-aryl radical of the formula in claim 1, has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are no biological assays described anywhere in the specification. There is no biological data of any sort for any of Applicants' compositions or compounds. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in photo therapy of human diseases is found in the passage spanning line 7, page 2 to line 2, page 3 of the specification.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h)

The scope of the claims involves all of the millions of compounds of claim 1 as well as the hundred of diseases embraced by the term "target tissue". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics*, 211 USPQ 907, *In re Langer*, 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

Applicants argue that they have provided numerous representative examples of such treatment. They also assert that the skilled physician could search for the


target tissue and thus determine which diseases to treat. This is not persuasive. Firstly, there are no working examples of any disease treatment in the specification. Secondly, brief description of how to search for is hardly the same as detailed description of how to use. Thirdly, performing the clinical trials on the millions of compounds embraced by the present claims would require a huge amount of experimentation. Thus, the amount of experimentation required to practice Applicants disease treatment claims would be excessive.

16. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The list of diseases that Applicants intend to treat is taken from lines 1-9, page 13. This passage of the specification does not deal with disease treatment but rather is part of the functional definition of radical "E". There is insufficient nexus between this structural definition on page 13 and disease treatment. The passages dealing with intended disease treatment were described above in the enablement rejection. Besides it is simply illogical that prostate, lung, colorectal, and brain tumors could

be treated by photo therapy. What would be the source of light on these organs located inside the body cavity?

Conclusion

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. After February 9, 2004, the Examiner may be reached at (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.


Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK